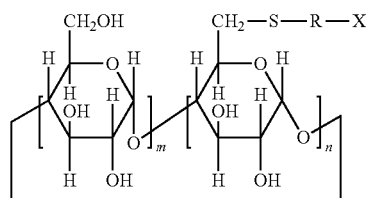


3

rapacurium, mivacurium, atracurium, (cis) atracurium, succinylcholine and tubocurarine.

It has now been found that 6-mercapto-cyclodextrin derivatives having the general formula I



Formula I

wherein m is 0-7 and n is 1-8 and m+n=7 or 8;

R is (C₁₋₆)alkylene, optionally substituted with 1-3 OH groups, or (CH₂)₆-phenylene-(CH₂)_p-;

o and p are independently 0-4;

X is COOH, CONHR₁, NHCOR₂, SO₂OH, PO(OH)₂, O(CH₂-CH₂-O)_q-H, OH or tetrazol-5-yl;

R₁ is H or (C₁₋₃)alkyl;

R₂ is carboxyphenyl;

q is 1-3;

or pharmaceutically acceptable salts thereof;

are highly active in vivo in the reversal of the action of neuromuscular blocking agents.

No protection per se is sought for the following 6-mercapto-cyclodextrin derivatives:

6-per-deoxy-6-per-(2-hydroxyethylthio)-β-cyclodextrin and

6-per-deoxy-6-per-(2-hydroxyethylthio)-γ-cyclodextrin, which are described by Ling, C. and Darcy, R. (J. Chem. Soc. Chem Comm. 1993, (2), 203-205);

6-mono-deoxy-6-mono-(2-hydroxyethylthio)-β-cyclodextrin, which is disclosed by Fujita, K. et al. (Tetr. Letters 21, 1541-1544, 1980);

6-per-deoxy-6-per-(carboxymethylthio)-β-cyclodextrin, which is described by Guillo, F. et al. (Bull Chem. Soc. Chim. Fr. 132 (8), 857-866, 1995);

6-mono-deoxy-6-mono-(carboxymethylthio)-β-cyclodextrin, which is described by Akiie, T. et al. (Chem. Lett. 1994 (6), 1089-1092);

6A,6B-dideoxy-6A,6B-bis[(o-carboxyphenyl)thio]-β-cyclodextrin and 6A,6B-dideoxy-6A,6B-bis (carboxymethylthiol)-β-cyclodextrin, which are described by Tubashi, I. et al. (J. Am. Chem. Soc. 108, 4514-4518, 1986; and

6-per-deoxy-6-per-(2,3-dihydroxypropylthio)-β-cyclodextrin, which is described by Baer, H. H. and Santoyo-González, F. (Carb. Res. 280, 315-321, 1996). These prior art 6-mercapto-cyclodextrin derivatives have been described in relation with different utilities in each instance.

However, the above mentioned prior art 6-mercapto-cyclodextrin derivatives do belong to the main aspect of the present invention which relates to the use of a 6-mercapto-cyclodextrin derivative according to the general formula I for the manufacture of a medicament for the reversal of drug-induced neuromuscular block.

In one embodiment the invention relates to 6-mercapto-cyclodextrin derivatives having the general formula I,

wherein m is 0-7 and n is 1-8 and m+n=7 or 8;

X is COOH, OH or CONHCH₃;

R is (C₁₋₆)alkylene or (CH₂)₆-phenylene-(CH₂)_p;

4

o and p are independently 0-4; or a pharmaceutically acceptable salt thereof, with the exclusion of

6-per-deoxy-6-per-(2-hydroxyethylthio)-β-cyclodextrin;

6-mono-deoxy-6-mono-(2-hydroxyethylthio)-β-cyclodextrin;

6-per-deoxy-6-per-(2-hydroxyethylthio)-γ-cyclodextrin;

6-per-deoxy-6-per-(carboxymethylthio)-β-cyclodextrin;

6-mono-deoxy-6-mono-(carboxymethylthio)-β-cyclodextrin;

6A,6B-dideoxy-6A,6B-bis[(o-carboxyphenyl)thio]-β-cyclodextrin; and

6A,6B-dideoxy-6A,6B-bis(carboxymethylthiol)-β-cyclodextrin.

The term (C₁₋₆)alkylene as used in the definition of formula I means a branched or straight chain bivalent carbon radical containing 1-6 carbon atoms, such as methylene, ethylene (1,2-ethandiy), propylene (1-methyl-1,2-ethanediy), 2-methyl-1,2-ethanediy, 2,2-dimethyl-1,2-ethanediy, 1,3-propanediy, 1,4-butanediy, 1,5-pentanediy and 1,6-hexanediy.

The term phenylene means a bivalent moiety the free valencies of which can be positioned either ortho, meta or para to one another.

The term (C₁₋₃)alkyl means a branched or straight chain alkyl group containing 1-3 carbon atoms, i.e. methyl, ethyl, propyl and isopropyl.

The term carboxyphenyl means a phenyl group which is substituted at either the ortho-, the meta- or the para-position with a carboxy-group. The ortho-carboxyphenyl group is preferred.

Compounds according to formula I wherein n+m is 7 are derivatives of β-cyclodextrin, those wherein n+m is 8 are derived from γ-cyclodextrin.

Preferred are the 6-mercapto-cyclodextrin derivatives of formula I wherein X is COOH, or a pharmaceutically acceptable salt thereof.

More preferred are the 6-mercapto-γ-cyclodextrin derivatives of formula I wherein n is 8, R is (C₁₋₆)alkylene and X is COOH.

Particularly preferred 6-mercapto-cyclodextrin derivatives of the invention are

6-per-deoxy-6-per-(2-carboxyethylthio)-γ-cyclodextrin;

6-per-deoxy-6-per-(3-carboxypropylthio)-γ-cyclodextrin;

6-per-deoxy-6-per-(4-carboxyphenylthio)-γ-cyclodextrin;

6-per-deoxy-6-per-(4-carboxyphenylmethylthio)-γ-cyclodextrin;

6-per-deoxy-6-per-(2-carboxypropylthio)-γ-cyclodextrin; and

6-per-deoxy-6-per-(2-sulfoethylthio)-γ-cyclodextrin.

The 6-mercapto-cyclodextrin derivatives of formula I can be prepared by reacting a C6-activated cyclodextrin derivative of formula II with an alkylthiol, arylalkylthiol or arylthiol derivative corresponding to H-S-R-X, wherein R and X